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SOME GENERAL FEATURES OF ENDOCRINE INFLUENCE ON METABOLISM.*

BY W. B. CANNON, M.D.,

BOSTON.

(From the Department of Physiology, Harvard Medical School.)

A FAIRLY constant or steady state, maintained in many aspects of the bodily economy even when they are beset by conditions tending to disturb them, is a most remarkable characteristic of the living organism. Though the blood is the common carrier for all manner of food material and for waste, its composition varies to a surprisingly slight degree. Though warm-blooded animals are exposed to numerous and extensive alterations of surrounding temperature, they themselves undergo shifts of temperature within only a brief range. And though food is taken in as it is provided or desired and is utilized as conditions may demand, the body weight of the full-grown individual continues for long periods on a strikingly even level. Since in these, and in other instances which could be added to them, circumstances are often present which, if not controlled, would profoundly modify the constancy of the state, we must assume that controlling factors are at hand ready to act whenever the constancy is imperilled. The existence of steady states in the body and some agencies maintaining them have, of course, long been recognized. On this occasion I am laying emphasis upon these states because of an interest in some tentative general considerations with regard to physiologic factors regulating them, and in the possible bearing of these considerations on problems of internal secretion. As they may have value in suggesting lines of research and bases for critical judgment, they may be worthy of attention.

Six Propositions Regarding Physiologic Factors Maintaining Steady States in the Body. The first proposition is that in an open system, such as our bodies represent, complex and subject to numberless disturbances, the very existence of a poised or steady state is in

* Read as one of the papers in a symposium on Internal Secretion, Congress of American Physicians, Washington, May 6, 1925.

itself evidence that agencies are at hand keeping the balance, or ready to act in such a way as to keep the balance. These agencies may act antagonistically, like the nerves of the heart. A tonic action is also possible, as in arterial vasoconstriction, with constancy provided indirectly, one step back, in a nerve center subjected to opposed control. The regulation may consist of a check on the excesses of a continuous function, like the respiratory setting of the carbon-dioxide level in the blood. Again, there may be limitation by overflow, a safety-valve arrangement, as in the renal thresholds of overflow or escape for various constituents of the blood.

A second proposition is that, if the state remains steady, there is an automatic arrangement whereby any tendency toward change is effectively met by increased action of the factor or factors which resist the change. Somewhat similar statements of this proposal have been made by Spencer¹ and also by the Belgian physiologist, Fredericq.² They did not recognize, however, failure of the state to retain its poise because of absence or weakness of a controlling agent—a not uncommon consequence of pathologic processes. For that reason I have made the statement conditional (“if the state remains steady”). As Lotka³ has pointed out, such a reservation, which is required for constant states in living beings, and which is a recognition of their lack of permanent stability, would sharply distinguish the proposal from the strict principle of Le Chatelier which was enunciated for physicochemical systems.

A third proposition is that any factor which operates to maintain a steady state by action in one direction does not act at the same point in the opposite direction. This declaration may appear tautological, but, as will be shown later, it has interesting bearings, and if its probable truth had been recognized it would have led to more cautious conclusions than have been drawn.

A fourth proposition, related to the third, is that factors which may be antagonistic in one region, where they effect a balance, may be coöperative in another region. It is necessary, therefore, to define closely the field of action of opposing factors in discussing a physiologic equilibrium.

A fifth proposition is that the system of checks which determines a balanced state may not be constituted of only two antagonistic factors; on either side there may be two or more, brought into action at the same time or successively. Further, the two may be of different nature, for instance, an internal secretion and a neuromuscular agency.

A sixth proposition is that when a physiologic factor is known which can shift a steady state in one direction, it is reasonable to look for a physiologic factor or factors having a contrary or counterbalancing effect.

In the foregoing statements the expression “ready to act” has

been used as an alternative to "acting" because in certain instances there is evidence that the situation is not kept balanced by direct and immediate opposition of active agencies, but is allowed to move to and fro within limits or within critical points, possibly under control of simple physicochemical adjustments, and only when these limits are passed are the more complex and indirect physiologic agencies (that is, those involving reactions peculiar to the organization of living beings) brought into play.

The advances in our knowledge of the relations of internal secretion to metabolism have lately been so great and so various that an attempt to present an encyclopedic survey in brief compass would be futile. Instead, may we not consider the six propositions, stated above, with regard to some recent investigations and results, and see to what degree interpretation is clarified thereby and new lines of work are indicated. In doing so I wish to disclaim any effort at an elaborate or final scheme of relationships. The concept of equilibrating factors will be used merely as a means of unifying some apparently diverse and separate observations which, in the main, have been personal experiences.

The Equilibrating Factors in the Blood-sugar Balance. Carbohydrate is the material most readily burned in the body. When it is provided in abundance the combustion of fat is almost completely stopped and the combustion of protein is reduced to a minimum. In less than half an hour after the ingestion of sugar the respiratory quotient usually rises to about 1.⁴ The concurrent testimony of investigators supports the conclusion that carbohydrate is not only the most readily utilizable source of energy, but is essential for working the mechanism of muscular contraction. Its importance, therefore, need not be emphasized.

In the economics of the body, problems arise concerning carbohydrate demand and supply because that foodstuff is continuously being used up and is renewed only periodically. When it is taken in and is being digested it must not be permitted to increase in the blood above 170 or 180 mg. per 100 cc., for then it will be lost by escape through the kidneys. The amount available is likely to be more than is needed for current uses; the excess must be set aside in storage, in a compact and not immediately utilizable form. This is accomplished chiefly in the liver, though there are, of course, the scattered local stores. When need arises the stored carbohydrate must be released from the liver, for if the glucose in the blood falls to approximately 45 mg., convulsions are likely to occur, which may be followed by coma and death. Thus, in sum, the blood-sugar level is an equilibrium between the supply and the demand, with storage as an adjusting arrangement. The normal outer limits of the equilibrium may be regarded as at approximately 180 mg. where loss occurs, and approximately 45 mg. where convulsions occur. But the normal variations of blood sugar are ordi-

narly well within these extreme limits. If our earlier propositions are correct, factors are at work, holding the oscillations inside the narrower confines. Some recent research done by McIver and Bliss and myself⁵ has revealed a sympathico-adrenal mechanism as one factor in the balance, protecting the body against the dangers of too low blood sugar.

As an indicator of increased adrenal secretion we have used the heart, disconnected from the central nervous system and left in the body to perform its function. If the temperature is kept normal, only changes in the blood stream can affect the rate. Alterations of blood pressure do not influence it, but a very slight increase in the adrenin content of the blood promptly makes the heart beat faster. Anrep and Daly⁶ have recently found that the denervated heart is sensitive to the presence of adrenin,* 1 part in 1,400,000,000 parts of blood. All investigators now admit that medulli-adrenal secretion is controlled by sympathetic impulses. Afferent stimulation and asphyxia, which are known to discharge sympathetic impulses, cause acceleration of the denervated heart—just such a change as is produced by increase of adrenin in the blood. The only agent which may confuse the response in an acute experiment is a substance given off from the liver after protein feeding—a source of trouble which can be made insignificant by study of a fasting animal or abolished by severing the hepatic nerves.⁷ If these precautions are taken the positive response disappears when the adrenal glands are removed or inactivated by nerve section. The faster heart rate, therefore, is then due to medulli-adrenal secretion.⁸ The results which we have obtained by use of the denervated heart have been questioned by Stewart and Rogoff.⁹ These results, however, have been confirmed by Tournade and Chabrol¹⁰ in Algiers, working with a crossed circulation; by Houssay and Molinelli¹¹ in Buenos Aires, also employing a crossed circulation; by Florovsky¹² and by Baschmakoff¹³ in Odessa, using the denervated salivary gland, by Hartman, McCordock and Loder¹⁴ in Buffalo, recording the reactions of the completely denervated iris; by Anrep^{15,16} in London, studying the denervated heart and kidney and also the isolated heart outside the body but connected with the abdominal aorta and inferior vena cava. Furthermore, Kodama¹⁶ in Sendai, Japan, repeating the procedure of Stewart and Rogoff, has found, not what they found, but what we found. Naturally Stewart and Rogoff¹⁷ have criticized Kodama's results, and have declared that he did not master their technic. A recent letter from Sendai, however, states that other workers there have refined the method, and that Kodama's data have been fully substantiated. If any investigator anywhere had given Stewart and Rogoff any support for their contention that adrenal secretion is

* The word "adrenin" is used to indicate the secretion of the adrenal glands "adrenalin" a preparation of the same.

constant, and unaffected by conditions which induce sympathetic activity, there might be reason for seriously considering it. But that support is lacking. Opposed to it is the concordant experience of other investigators, derived from a variety of methods. It justifies confidence in the results obtained by use of the denervated heart as a signal for greater discharge from the adrenal medulla.

Now to return to the question of a sympathico-adrenal factor working to keep the blood sugar normal and to protect the organism from dangerous hypoglycemia. Among the hypoglycemic reactions which occur when an excessive dose of insulin has been given are pallor, a rapid pulse, dilatation of the pupils and profuse sweating. These are phenomena resulting from sympathetic impulses. The denervated heart tells whether the adrenal medulla shares in this increased activity. When, after an injection of insulin, the glycemic concentration is falling, it reaches a critical point at which the denervated heart begins to beat faster. And as the sugar percentage continues to fall the heart rate continues to rise until a maximum is reached. In the unanesthetized test animal the critical point lies between 70 and 80 mg. of glucose per 100 cc. of blood—a concentration at which in man also hypoglycemic symptoms first appear.¹⁸ The faster beating of the denervated heart indicates that medulli-adrenal secretion has been stimulated. That inference is verified by removal of the glands, or by removal of one and denervation of the other, whereupon a fall of the glycemic percentage below the critical point is not accompanied by a more rapid heart beat. The faster beating of the heart, of course, indicates that impulses are being discharged along splanchnic fibers. These sympathetic impulses, in coöperation with increased adrenal secretion, might be expected to call forth sugar from the liver. This inference is confirmed by the fact that as the rate of the denervated heart increases (manifesting sympathico-adrenal activity), the rate of falling of the glycemic percentage is checked. And if not too much insulin has been given, the glycemic percentage may not only cease dropping, but may rise to normal. A highly significant feature of this sympathico-adrenal activity is that as the blood-sugar level rises the activity subsides. Indeed, when glucose is injected intravenously the activity has been seen to subside completely within two minutes.

Here is a remarkable mechanism having the function of keeping up the physiologic percentage of blood sugar when there is danger of deficiency. After a dose of insulin the mechanism may be brought into service hours before a convulsion occurs, and if effective it may wholly protect against a convulsion. From the evidence provided by these observations we may conclude that the lower inner limit of variation of blood sugar, when the sugar is being withdrawn, lies in the region of 70 to 80 mg. Reduction below this limit calls into action a sympathico-adrenal factor work-

ing to prevent further reduction. This factor works with increasing vigor the lower the glycemic percentage, until an acme is reached in a convulsion, when the denervated heart beats most rapidly.

According to Olmsted and Logan,²⁰ the convulsive seizures do not occur in a spinal animal, even when the glycemic percentage is extremely reduced. The sensitive region appears to be in the medulla or midbrain, for, in decerebrate animals typical convulsions result from hypoglycemia. Rapport and I²¹ have shown that a center for medulli-adrenal secretion exists in the fore part of the floor of the fourth ventricle. Quite possibly this region is especially sensitive to a reduced sugar supply and by sympathico-adrenal discharges (culminating in spasms) protects the rest of the body against the hazards of too great a reduction.

Our results have received support from Abe,²² who made use of the sensitized iris to signal a greater output from the adrenal medulla. In some instances he noted no effect, or very slight effect, during the first half-hour after giving insulin. Then there was a sudden change, marking the onset of the sympathico-adrenal function as the blood-sugar percentage fell. Houssay, Lewis and Molinelli²³ also have supported our conclusions. They employed a crossed circulation from the left adrenal vein of one dog to a jugular vein of another. When an insulin hypoglycemia was established in the donor, hyperglycemia was produced in the recipient—a result which did not occur if the left splanchnics of the donor had previously been severed. Both methods showed that adrenal secretion was increased by hypoglycemia, but unfortunately they were not used in such a way as to bring out the evidence for the critical point at which the sympathico-adrenal mechanism is set going, an observation of special interest in relation to the glycemic equilibrium.

In our second proposition we postulated that the preservation of a balanced state implies an automatic arrangement whereby a tendency to change is met by increased action of a factor or factors which resist the change. We have surveyed the evidence for a factor checking a shift of the glycemic equilibrium downward. What agency or agencies operate in the opposite sense, to prevent a shift upward, toward a high sugar concentration? The answer might be given promptly that it is the internal secretion of the pancreas, if competent investigators had not concluded that insulin administered to normal animals is capable of decreasing hepatic glycogen, that is, that insulin may work in the same direction with the sympathico-adrenal mechanism. There is excellent reason for believing, however, that insulin primarily is the opposing factor and that its apparently anomalous effect in normal animals should be regarded as a secondary phenomenon. Let us examine the basis for the inference that the internal secretion of the pan-

creas, or insulin, normally protects the body against hyperglycemia by promoting sugar storage in the liver:

1. There is the outstanding fact that removal of the pancreas is promptly followed by hyperglycemia and a great reduction in the hepatic glycogen reserve. This phenomenon is so well known as to need no emphasis.

2. As Banting and his collaborators²⁴ have shown, the administration of insulin to depancreatized animals not only brings the blood sugar down to the normal level, but causes glycogen to accumulate again in large amounts in the hepatic cells. Indeed, the hepatic glycogen of insulin-treated diabetic animals may be considerably more than in normal well-fed controls.

3. It has been found that insulin will induce a deposit of glycogen in the liver when the blood sugar is within the range of normal variations. Thus, Cori²⁵ has recently reported that the amount of hepatic glycogen may be quadrupled in phlorizinized rabbits by repeated doses of insulin.

4. Finally, as bearing on the antagonism between the glycogenolytic action of adrenin and the glycogenetic action of insulin, there may be cited the experiments of McCormick, Noble and O'Brien.²⁶ They discovered that when large doses of adrenalin were injected—doses which produced a marked reduction of hepatic glycogen in control animals—the additional injection of insulin was accompanied by a striking retention of the hepatic glycogen. The excessive doses of adrenalin used by them (for example, 2.5 cc. in a rabbit) allowed, they state, “enormous quantities of insulin” (for example, 140 units) to be tolerated without convulsions.

All these various observations bear witness to the importance of the internal secretion of the pancreas (insulin) as an agent operating conversely to the sympathico-adrenal mechanism in affecting the glycemic percentage by action on the liver.

The suggestion that insulin does not act in one direction only but in both directions on the liver (that is, glycogenetically and glycogenolytically) has, to be sure, been derived from experiments on normal animals. McCormick and Macleod²⁷ gave insulin and carbohydrates to rabbits rendered free of glycogen and found that less glycogen was deposited in the livers of the insulin-treated animals. Dudley and Marrian²⁸ compared the livers of glycogen-rich mice and rabbits, some of which had received insulin and others left as controls; the hepatic glycogen of the former was very greatly reduced as compared with the latter. Babkin²⁹ also has reported that the glycogen content of the liver in well-nourished rabbits which had been given insulin is markedly lowered. The comments on these experiments have been somewhat equivocal. Thus Macleod³⁰ states that “There can be no doubt that insulin causes a rapid reduction in the amount of glycogen in the liver,” but he also remarks later that at some stage after the blood sugar

has become reduced by insulin, "The glycogenolytic process in the liver is stimulated." A similar suggestion was offered by Dudley and Marrian. In our third proposition we intimated that a factor does not have opposed functions with reference to the equilibrium which it protects. If we keep that idea in mind and remember that hypoglycemia calls forth sympathico-adrenal service, the results above detailed can be reasonably explained. It is significant that in the experiments of McCormick and Macleod, despite an effort to give doses of insulin "just insufficient to cause convulsions," convulsions occurred in 6 out of 15 cases; in the experiments of Dudley and Marrian the animals were killed on the appearance of convulsions; in the experiments of Babkin, though "convulsions were not observed," the glycemic percentage was far below the critical level. In all these experiments, therefore, the conditions were such that the hepatic glycogen stores were being drawn upon, not by direct action of insulin, but by the direct action of the factor opposed to insulin—the sympathico-adrenal factor—made to operate powerfully by the insulin hypoglycemia. This conclusion is supported by the testimony by Burn³¹ that a small dose of insulin, mildly effective in the normal animal, causes in an animal treated with ergotamin profound hypoglycemia, with convulsions and collapse; for ergotamin, though having no influence on the action of insulin, paralyzes the protective sympathico-adrenal reaction. That the secreted adrenin plays an important part in this reaction is proved by the fact that the fall of the glycemic percentage is not checked, or is only slightly checked, at the critical point, if the adrenals have previously been inactivated,⁵ and also under such conditions by the appearance of convulsions sooner and after smaller doses of insulin than in animals with active glands—a phenomenon observed by Sundberg,³² by Lewis³³ and by us.⁵

From all the foregoing evidence it appears that the normal level of blood sugar is preserved by the sympathico-adrenal factor acting on the low side of the equilibrium and by the pancreatic factor and the renal overflow acting on the high side. Much still remains to be learned regarding the conditions bringing the islands of Langerhans into play. From the experiments of Banting and Gairns,³⁴ the inference may be drawn that a nervous control of insulin secretion is not necessary. That does not prove, however, that nervous control does not exist and could not be useful—the innervation of the heart is not *necessary*! The observations of De Corral³⁵ and of McCormick, Macleod and O'Brien³⁶ point to vagus impulses as causing a discharge of insulin into the blood stream. Recent (unpublished) studies by Britton at the Harvard Physiological Laboratory, as well as the investigations of Clark,³⁷ have corroborated the earlier evidence. In harmony with these results are those announced by Lewis and Magenta,³⁸ that after section of the abdominal vagi a given dose of insulin is less effective than before.

Because in the presence of high glycemic percentages remnants of the pancreas degenerate,³⁹ and the islet cells show signs of overwork,⁴⁰ it seems probable that just as the adrenals are stimulated by hypoglycemia, so likewise the "islands" are stimulated by hyperglycemia, that is, that each secretion is involved in a righting response which restores the normal equilibrium. If further research proves that the vagus provides a fine adjustment for insulin secretion, as the sympathetic does for adrenal secretion, it will be peculiarly interesting because of the common opposition between vagal and sympathetic functions.

A caution appears to be necessary here lest the ideas just expressed be taken as confirming Zuelzer's theory of the adrenal origin of diabetes. Indeed, Stewart⁴² has declared that my interpretation of the sympathico-adrenal service in maintaining the normal glycemic concentration is only an elaboration of that theory. The essence of Zuelzer's theory was that the adrenals and the pancreas are such aggressive antagonists that when the pancreas is removed diabetes follows because of the unchecked action of the adrenals. The theory has no sound basis. And our observations, that sympathico-adrenal activity, roused by hypoglycemia, is promptly checked by hyperglycemia and that it is made to work again only when the blood sugar has *fallen* well below the usual level, should have prevented anybody from imagining that our experiments in any sense support Zuelzer's idea. Instead, they raise the question whether the high sugar level of diabetes may not be associated with a depression of sympathico-adrenal function.

It will be recalled that in our fifth proposition we suggested that when opposed factors assure an equilibrium there may be more than one on either side. Indeed, a primary action of the islands of Langerhans and the coöperative overflow arrangement in the kidneys may be regarded as a double device preventing a rise in the glycemic level. On the other arm of the balance may be placed the testimony of Olmsted and Logan,²⁰ that the pituitary body is important. They state that typical convulsive seizures occur in decerebrate animals if the pituitary body has been removed, but that otherwise even massive doses of insulin fail to lower blood sugar to a marked degree. This result has been associated with the observation by Burn,³¹ that pituitrin can lessen or entirely prevent insulin hypoglycemia. The conclusion that the posterior lobe of the pituitary may collaborate with the adrenal medulla thus seems justified. In a recent investigation, however, Bulatao and I⁴³ have shown that in decorticated animals with intact pituitary glands insulin regularly causes a drop in the glycemic concentration, and we have called attention to the same phenomenon in three similar cases described by Olmsted and Logan. Furthermore, we showed that in decorticated and decerebrated animals sympathico-adrenal activity may be maximal and may therefore retard or lessen

the effect of insulin. For Olmsted and Logan to conclude on the basis of their few cases, which are not decisive, that the high blood sugar after decerebration is maintained by pituitary influence, seems to us unwarranted. In other words, though pituitrin as a pharmacodynamic agent inhibits the action of insulin, proof is still lacking that a pituitary secretion as such has that effect, and could cooperate with adrenal secretion.

Because of the effects which hypothyroidism, hyperthyroidism and thyroid feeding have in disturbing the glycogen content of the liver and influencing sugar tolerance,⁴⁴ and also because of reported hypersensitiveness of thyroidectomized animals to insulin,⁴⁵ it may be that the thyroid normally collaborates with the sympathico-adrenal apparatus. The evidence on this point is still too vague and uncertain, however, to justify discussion of it in this paper.

In our fourth proposition we mentioned that factors opposed in one region of the body may be collaborators in another region. This is perhaps the case with adrenin and insulin. They are opposed with respect to glycogen storage in the liver. They may be collaborators, however, in the utilization of sugar in muscles. Various investigators have found that injected adrenalin accelerates metabolism,⁴⁶ and recent Harvard studies have proved that secreted adrenin has the same effect,⁴⁷ and that the effect occurs when the circulation is almost wholly confined to muscles (not yet published). Adrenin causes in the isolated heart not only a greater consumption of oxygen per unit of time but also may cause total disappearance of the stored glycogen.⁴⁸ Hepburn and Latchford⁴⁹ observed that insulin accelerates removal of glucose from the perfusing fluid by the isolated mammalian heart, and Burn and Dale⁵⁰ noted that insulin causes rapid removal of glucose in a decapitated and eviscerated preparation, that is, when the heart and skeletal muscles are the only important metabolizing organs. The early stages of insulin action in such a preparation are characterized by increased oxygen consumption, with a respiratory quotient of unity. Thus insulin and adrenin, antagonists in the liver, appear to be collaborators elsewhere. Insulin may promote everywhere the passage of sugar from the blood into cells. In muscle cells adrenal secretion may work with insulin to facilitate the chemical changes underlying contraction. All this, however, remains to be proved. The suggestion is mentioned here merely to illustrate the possibility of different relations of physiologic agents at different places in the organism.

Some Hints at Factors Affecting Protein Equilibria. Protein is quite as important as carbohydrate for bodily welfare and function. It is necessary for such invaluable services as building the cellular structure of the organism, repairing or restoring the worn or wasted parts, and providing the essentials for coagulation and for normal composition of the blood. It is constantly being dis-

integrated and lost from the body, and the possibility of securing a new supply is not always at hand. Since there is an elaborate arrangement for storing excess of carbohydrate and for liberating it as required, it would appear reasonable to look for a similar arrangement for storing indispensable protein against a time of need. The process of deaminization and the excretion of extra nitrogen indicate that accumulation of protein must be limited. The existence of a nitrogen equilibrium, capable of being altered and adapted to the requirements of the organism, implies that there prevails an orderly regulation for riddance or retention and the maintenance of a steady state.

The reality of a reserve or "deposit" protein has often been debated. Gradually there has developed a considerable body of evidence that with abundant protein feeding the hepatic cells can store protein just as they can store glycogen. More than forty years ago Afanassiew⁵¹ noted that if "albuminates" were fed to dogs the liver became firm and resistant, and the hepatic cells increased in size and contained between their protoplasmic strands many fine sharply outlined granules, protein in nature. Seitz⁵² brought further support, finding that in fed animals the total nitrogen of the liver in relation to that of the rest of the body was from two to three times as great as in fasting animals. The observations of Berg⁵³ have been especially significant. In 1914 he reported that in the hepatic cells of animals which are given protein there appear numerous small droplets or masses which are clearly distinguishable from the cell structure, which react as protein to Millon's reagent, which are caused to disappear by fasting, and which are restored only when protein or amino-acids are fed. In 1922 he showed that these droplets can be distinguished in fresh teased-out liver cells stained with neutral red, and that they give the ninhydrin reaction of the simpler proteins. Berg's earlier observations have been fully confirmed by Stübel⁵⁴ and by Noel.⁵⁵ This histologic evidence for a protein reserve has been corroborated by Tichmeneff's chemical studies.⁵⁶ He starved mice for two days, then killed half of them and after giving the others an abundance of cooked meat killed them and compared the livers of the two groups. Expressed in percentage of body weight, the livers of the meat-fed animals had increased about 20 per cent, with the hepatic nitrogen content augmented between 53 and 78 per cent.

The concept of storage of valuable material involves the idea not of miserliness but of service—the appropriate use of the material outside the storage place. There appears to be at present no proof that protein is taken from the liver for use in another part of the body which requires restoration or improvement, though the possibility that such a transfer could occur would justify an attempt to search for it. There is testimony, however, to a function which the liver performs in maintaining the protein constituents of the

blood. Kerr, Hurwitz and Whipple⁵⁷ found that after depletion of blood plasma (by bleedings and injections of washed blood corpuscles in Locke's solution) the restoration of the serum protein is delayed if the liver has been damaged or has been sidetracked by an Eck fistula. Furthermore, liver injury is associated with a fall in the serum proteins. Although in the blood of the normal animal fibrinogen is rapidly re-formed after being removed, Meek found that it fails to be re-formed if the liver is unable to act.⁵⁸ It seems, therefore, that the liver plays a fundamental role in the production of fibrinogen. In the production of antithrombin or antiprothrombin as well, and possibly of heparin also, there are indications that the liver is concerned and thereby might influence deeply the coagulation of the blood.

The serum proteins remain at a remarkably steady concentration, fluctuating only slightly with fasting, feeding, health or disease. And yet, as shown above, when they are reduced the liver soon restores them. Again the factors concerned with blood clotting are ordinarily in balance, so that coagulation takes a moderate and fairly uniform time. The relations can be disturbed, however, so that the time is longer or shorter. In experiments by Gray and myself⁵⁹ we obtained records of a shortening of the clotting time of blood by adrenalin injections if the blood is allowed to circulate through abdominal organs; the phenomenon fails if the circulation is confined above the diaphragm or if the intestines and liver have been removed. Increased adrenal secretion induced by splanchnic stimulation or excitement has a similar effect, as shown by experiments done in coöperation with Mendenhall.⁶⁰ According to Grabfield,⁶¹ adrenalin increases the prothrombin element in the blood. It is significant that blood taken at the height of the hypoglycemic reaction, when sympathico-adrenal activity is maximal, "clots almost immediately it is withdrawn," as Macleod³⁰ has remarked, and as we also have noted. Finally, as Gray and Lunt⁶² showed, a large hemorrhage hastens the coagulation of blood if the liver (and intestine) is in the circulation, but not if the blood flow is excluded from the abdomen. Since the sympathetic is stimulated by considerable hemorrhage, probably sympathico-adrenal action is normally involved in the response.

Additional evidence that the protein material of the liver can be called out by appropriate stimulation was furnished by Stübel,⁵⁴ who found that the deposited droplets or small masses in the hepatic cells could be greatly reduced by injecting adrenalin subcutaneously. Moreover, in collaboration with Uridil and with Griffith,⁶³ we have shown that after protein feeding, stimulation of the nerves of the liver causes discharge of a still undetermined substance which accelerates the heart and causes a noteworthy increase of arterial pressure. The phenomenon is reduced to insignificance

in animals which have been fasting, or which have been fed carbohydrate or fat.

From the foregoing observations we may conclude that the liver is an organ of central importance not only for carbohydrate, but also for protein metabolism. It shares with other parts the power of constructing protein from amino-acids, but when large amounts of protein are fed it lays by a reserve or deposit to a much greater degree than do the other parts.⁵⁶ This reserve can be called out by sympathetic stimulation and by adrenin. In maintaining the normal consistency and coagulability of the blood the liver is indispensable. Here are steady states in which the liver performs quite as important a task as it performs in the carbohydrate balance of the body, and probably the factors which control the situation act with quite as great a degree of nicety. Unfortunately we are still in a twilight zone which surrounds the problem, and vision is not clear. Hints have been given as to factors affecting the protein levels, but much work must still be done before we shall be well informed regarding them or their ways of producing steady states.

An Endocrine Factor Operating to Maintain the Temperature Equilibrium. The uniform temperature of warm-blooded animals, though they are exposed to very different environmental temperatures, has already been alluded to as an outstanding example of physiologic constancy. The temperature equilibrium is maintained by opposing factors. Concerning the nature of the physical factors, vasodilatation and sweating, which operate when the body temperature tends to rise, there has been no difference of opinion. On the other hand, factors which are set in action when the temperature tends to fall have been the subject of discussion for more than a third of a century. Speck,⁶⁴ Loewy,⁶⁵ Johansson⁶⁶ and Sjöström⁶⁷ have concluded from experiments in which subjects were exposed to cold surroundings that the increased metabolism which results is to be explained wholly in terms of shivering or other muscular contraction. Voit,⁶⁸ Rubner⁶⁹ and recently Leonard Hill and his co-workers,⁷⁰ on the contrary, have conducted experiments in which subjects were similarly exposed to cold surroundings, but usually for long periods, and have found acceleration of the metabolic rate with no demonstrable muscular movements. "It is incomprehensible," Rubner wrote, "that many physiologists can still doubt the presence of this powerful regulating mechanism. And it is just as incomprehensible that the increase of heat in the presence of cold is ascribed solely to the gross shivering of the animal." What the nature of the chemical regulator is he did not suggest.

When warm-blooded animals are exposed to cold, the striking reactions are erection of hairs or ruffling of feathers, constriction of peripheral vessels and increase of blood sugar. These are signs that the sympathetic division of the autonomic system is in action.

Is secretion from the adrenal medulla augmented under these conditions? The answer to this question has interesting bearings on the old controversy regarding chemical control of body temperature. Since 1906 various observers have found that adrenalin stimulates oxygen consumption in isolated organs or in the body as a whole. This pharmacologic evidence was given a physiologic significance when Aub, Forman and Bright,⁷¹ at the Harvard Physiological Laboratory, found that if the adrenal glands are removed, though blood pressure and the body temperature remain unchanged, the metabolic rate may drop as much as 25 per cent below the previous normal level, and when later McIver and Bright⁴⁷ demonstrated that increased adrenal secretion accelerates the oxidative processes of the body. Clearly, if cold excites a greater outpouring of adrenin into the blood stream it would induce a faster burning in the body just when there would be need for it.

Cramer⁷² and Fujii⁷³ have reported reduction of the chromaffin substance of the adrenal medulla in animals exposed to low temperatures, but that condition, as Trendelenburg⁷⁴ has suggested, may not have resulted from overdischarge but from underproduction. More direct evidence of an increased medulliadrenal secretion brought on by cooling was obtained by Hartman and his collaborators.⁷⁵ Using the completely denervated iris of the cat to signal greater discharge of adrenin, they observed that dilatation of the pupil resulted when the cats were dipped in cold water or when they were dipped in warm water, and while wet were placed in a cold room or exposed to a current of cool air. The dilatation failed to occur if the adrenal glands were removed or inactivated. The use of the iris by Hartman has been severely criticized by Stewart and Rogoff,⁷⁶ who, however, have not used the completely denervated structure themselves. They have, therefore, no good basis for judgment. Because Hartman's results have been doubted, and also because we desired to eliminate quite certainly any emotional element (which wetting may have roused in the cat), Querido and I⁷⁷ have investigated the reaction by other methods.

As in other experiments, we have employed the denervated heart as an indicator of augmented adrenal secretion. We tried several different modes of exposing animals to cold before we hit upon the one which proved most satisfactory—that of introducing into the stomach a known amount of ice-cold water. The body heat of the animal passes into the cold fluid, and, unless the temperature is to fall, heat production must be increased to compensate for the loss. We have called the situation confronting the organism under the circumstances its “heat liability.” Obviously, since the weight, the temperature and the specific heat of the water are known, the number of calories which the animal must conserve or produce, or both, in order to prevent a temperature fall, can be calculated and nicely adjusted to the purposes of the experiment.

When heat liabilities varying between 1050 and 2400 small calories per kilogram were established there were invariably faster rates of the denervated heart, ranging from 15 to 64 per cent increase. When the adrenal glands were inactivated, and similar heat liabilities were presented to the organism, the increases ranged between 2 and 6 per cent only. And if, instead of ice-cold water, water near the body temperature was used the percentage increase was negligible. Since cold slows the rate of the isolated heart, the faster rate which follows the introduction of cold water occurs in spite of adverse conditions, a true physiologic response. And since this response fails when the adrenal glands are not acting, the inference is justified that the faster heart rate is a consequence of greater adrenal secretion.

If the heat liability is more than 1000 calories per kilogram acceleration of the denervated heart is almost uniformly attended by shivering. Thus, two calorigenic factors, secreted adrenin and muscular movements, are coöperating to protect against a shift of the temperature equilibrium toward the low side. But the shivering factor is not an essential part of the reaction, for if a heat liability of only 900 calories per kilogram is to be met shivering rarely occurs; if it occurs it is of short duration. The heart rate is faster, however, showing that the adrenal factor is operating.

The increase of adrenal secretion when the organism is exposed to the danger of too rapid heat loss, and the ability of naturally secreted adrenin to accelerate heat production, point to a physiologic reaction the services of which to the organism ought to be demonstrable. To test the capacity of this reaction we have studied the effect of a certain heat liability on shivering when the adrenal glands were active or inactive, and we have observed the influence of heat liability on the metabolic rate in the absence of shivering.

I have already remarked that if a heat liability of 900 calories is presented to the organism (cat) shivering rarely occurs or is brief. In 15 cases shivering occurred only twice and lasted in each instance only three minutes. In 15 cases in which the adrenals were inactivated by removal of one gland and denervation of the other the same heat liability per kilogram caused shivering in 13, and furthermore the shivering usually lasted considerably longer than in the control series—for six, seven, eight, eleven, thirteen and even sixteen and seventeen minutes instead of three minutes. Thus the primary protection against a heat deficit in the body is found in activities of the sympathetic system (erection of hairs, vasoconstriction, liberation of easily combustible sugar and discharge of adrenin), for these responses occur before shivering occurs and may be the only manifestation of the influence of a heat liability. If animals have been deprived of the calorigenic service of the adrenal medulla, however, greater demands are made on

muscular activity as a means of maintaining the normal temperature. Under normal conditions, therefore, two lines of defense are erected against a shift of the temperature equilibrium toward the low side. The first line is the sympathico-adrenal mechanism; if that fails and the temperature tends to drop in spite of it, the second line, muscular action or shivering, is invoked to produce the needed heat. And just as the convulsive seizures in hypoglycemia are attended by a greater adrenal discharge, so likewise is shivering due to cold thus attended. In both circumstances the introduction of the muscular factors marks a climax of the action of the automatic arrangements for defense.

If the foregoing inferences are correct it should be possible to demonstrate a faster metabolic rate in response to a bodily need for heat, quite apart from any muscular quiverings or contractions. To secure evidence on this point Querido and I, and later Bright, Britton and I, have studied the change in the metabolic rate in human beings when a known heat liability was created by taking ice-cold water or that combined with ice. We have now 19 satisfactory observations on 12 different subjects. The heat liability ranged from 360 to 512 small calories per kilogram. The metabolic rate has increased in these cases as much as 35 per cent, though the usual increase was not more than 17 per cent, and this without any sign of shivering either objective or subjective. Commonly the first effect of taking the cold water is a drop in metabolism, which is followed by the rise, which reaches its maximum at periods averaging twenty-five minutes after the liability was established.

The observations described above have direct bearing on the old controversy regarding the nature of the chemical agencies which help to preserve the temperature equilibrium of warm-blooded animals. Careful examination of the records of the experimenters who have argued that muscular contraction alone is the source of needed heat shows that they reported substantial increases of metabolism unattended by shivering. Furthermore, they failed to recognize that shivering may coëxist with and effectively mask a true chemical calorigenesis. And finally they have inferred that because a chemical mechanism did not operate in certain short experiments the mechanism does not exist—an inference having slight value when confronted by good evidence to the contrary. The results of our experiments are definitely opposed to the idea that a single factor, the muscular factor, is relied upon to keep the temperature balance from tipping downward. They bring support to the testimony and the argument of Voit and of Rubner, and offer an explanation of the chemical regulatory device which they postulated.

The evidence which has just been presented is not to be taken as excluding still other coöperating agencies. The fact that thyroid

activity accelerates metabolism, that thyroid removal lowers the metabolic rate and renders one more sensitive to cold, that the thyroid gland is probably subject to sympathetic control,⁷⁸ that it enlarges in animals exposed to low temperature,⁷⁹ that in the compensatory hypertrophy of a remnant the evidences of hyperactivity are greater if the animal is exposed to frigid surroundings⁸⁰—all these observations are highly significant of possible sympathico-thyroid collaboration in the upkeep of body temperature. As Aub⁸¹ has suggested, the sympathico-adrenal service may be employed for quick action and the thyroid may act in the same direction, but for more enduring needs. But here we must have more facts before we are warranted in giving thyroid function definitely a place among the compensatory factors evoked by a threatened shift in the temperature equilibrium.

In the foregoing discussion I have used to a large extent the results obtained in personal investigations. This emphasis will not, I trust, be interpreted as implying an overvaluation of the subjects studied or of the results achieved. It seemed best to rely on first-hand experience rather than to summarize the work of others. Furthermore, I wished to illustrate the interest which is added to a search for new facts if certain general ideas are allowed to suggest the direction of the experimenter's imagination and his efforts at securing insight.

In stating the first of the six propositions, that is, that a steady condition in the body implies physiologic agencies serving to maintain it, I mentioned several types. The type of opposed agencies has been illustrated by the operation of the sympathico-adrenal and the probable vago-insular mechanisms in keeping normal the blood-sugar level, and also by the regulation of the temperature equilibrium by physical and endocrine factors. The outflow or escape type has been illustrated by the function of the kidneys when there is too great a rise in the glycemic percentage. Questions at once appear as to other constant metabolic states, such as the storage and disposal of nitrogen, the laying by of fat, and the constancy of the organic and mineral constituents of the blood. In all these equilibria what agents are at work to limit the variations? What types do they represent? Though there are hints of answers to these questions, reliable information must still be sought.

The second proposition, it will be recalled, postulated corrective activity whenever an equilibrium is disturbed. This service was rendered, as we have seen, by the sympathico-adrenal apparatus in the presence of both hypoglycemia and hypothermia. If this second proposition is generally true, not only must we look for agents which protect a steady state from serious disturbance, but also we must search for the control which makes them act with

greater vigor, the more serious the disturbance. Related to this adjusted response is the fifth proposition: That accessory protective functions may be expected to coöperate if the primary functions fail. We have seen this situation in the coöperative activity of the kidney and the pancreas in resisting hyperglycemia, we have seen it also in the vasoconstriction, the increased adrenal secretion and the shivering which constitute progressively the three lines of defence against a drop in the temperature level of the body. We should keep our minds alert, therefore, not only for regulators of steady states but for the government of the regulators, and for the combination of regulators working toward the same end.

A general inquiry, important for clear understanding of body organization, would be one directed toward determining, so far as possible, the primary or immediate agencies, as contrasted with the secondary agencies, which induce a change of state. For example, we have seen that sympathico-adrenal stimulation is an immediate cause of glycogenolysis. Obviously any other condition inducing glycogenolysis may act, not directly on the liver, but through the sympathetic approach. Until the primary factors are known and properly recognized we are sure to have confusion—such confusion as is implied in the idea that a corrective agent operates in both directions at the same point.

In my opinion an attempt at present to develop an elaborate and intricate conception of the interrelations of the endocrine glands would be altogether premature and might be quite misleading. The necessary factors are not at hand. But the idea that endocrine factors play an important rôle in establishing and maintaining physiologic equilibria is reasonable and moderate in its scope, and does not involve a far-reaching projection of theory into the unknown. That the idea has value not only in raising questions regarding the existence and nature of balanced states but also in suggesting ways in which endocrine agencies may affect these states has, I hope, been made evident by the instances which I have cited.

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